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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Report On The Slide Review Of The 2,4-D Studies

TO: Jill Bloom
Special Review Branch
Special Review, Re-registration Division, H7508C

FROM: Marcia van Gemert, Ph.D. M. van Gemert 4/24/89
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THRU: William Burnam
Acting Director, HED, H7509C W J Burnam 4/24/89

Chemical: 2,4-D

Caswell No. 315

In the July 15, 1988 memo from M. van Gemert to M. McDavitt the Toxicology Branch requested that the Industry Task Force on 2,4-D Research Data (ITF) submit the kidney slides from the relevant subchronic and chronic/oncogenicity mouse and rat studies on 2,4-D for review by an independent pathology laboratory. The ITF had stated that the kidney lesions seen in these studies showed that an MTD had been reached in both studies.

The slides from the following studies were submitted to EPA and reviewed by Experimental Pathology Laboratories (EPL) under contract to EPA.

1. Subchronic rat study # 2184-102
2. Subchronic rat study # HET K-002372-103
3. Chronic study in rats #HLA-2184-103
4. Subchronic mouse study #HLA-2184-100
5. Chronic toxicity study in mice #HLA 2184-101

The five final reports from EPL have been received and are enclosed. EPA's consultant pathologist Dr. Lynnard J. Slaughter reviewed the final reports and wrote a memo dated 4/6/89. His conclusions are as follows, and his memo is attached:

1."The kidney lesion described and discussed in the above-mentioned reports are not life threatenig nor are they biologically important with respect to these animals' consumption of 2,4-D. These lesions are consistent with those found in aging rats. Whether or not the chemical in question influenced the early onset of a naturally occurring disease process cannot be deduced from animals subjected

to the experimental design that was used for these studies.

2. It is reasonable to expect that in life-threatening situations one or more appropriate organ function tests (kidney in this case) must be evaluated before it be concluded the animals' kidneys have failed or are failing. The following kidney function tests (clinical pathology) data presented in the original bioassay reports indicate that the blood urea nitrogen levels in these animals was decreased at the 14 mg and 45 mg dose levels.

The urinalysis, chemical and microscopic data of these animals needs evaluating. Also the total protein, total bilirubin, total cholesterol, SGOT and the SGPT serum values from the animals likewise need evaluating.

e. The kidney lesions identified in the above-mentioned pathology reports of test and control rat are commonly observed in 18-to 24-month-old animals that are progressively developing spontaneous chronic renal disease, the etiology of which remains unclear."

Concerning Dr. Slaughter's comment #2, the subchronic rat study HET K-002372-22 could not be found in the Agency to examine the clinical chemistry values as well as the urinalysis and this should be examined before a final determination can be made. However, in the two other subchronic studies in rats and mice no evidence of a confirmatory pathological nature was seen to indicate that the MTD had been reached in either the rat or mouse.

Conclusions:

The pathology reports on the review of the kidney slides indicate that the kidney lesions seen are those commonly observed in older rats and mice and are not life-threatening. Unless the ITF can provide convincing clinical chemistry evidence that the two studies were tested at doses sufficiently high to measure 2,4-D's oncogenic potential, both the rat and mouse chronic/oncogenicity studies will have to be repeated.

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Chemical: 2-4,D

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